Consequences of immunosuppression after pediatric liver transplantation

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Chapter 1

Introduction and outline of the thesis

The first human liver transplantation was performed by Thomas Starzl in Denver in 1967. The recipient was a 3-years old boy with biliary atresia, who died during the transplantation because of severe bleeding.[1] The first successful orthotopic liver transplantation with a survival beyond the immediate perioperative period, was performed in a 1.5-year old girl with a hepatocellular carcinoma in 1967.[2] She survived for more than one year, but nevertheless liver transplantation remained an experimental therapy with an 1-year survival of only 30%.[3] One of the reasons of early graft loss was uncontrollable rejection. **Immunosuppression in the early years con**sisted of high-dose steroids with 6-mecaptopurine and in later years azathioprine. The introduction of Cyclosporin A (CsA) in 1979 resulted in an profound increase of survival.[4;5] In 1983, liver transplantation was declared an accepted treatment for end stage liver disease for adults as well as children during the National Institute of Health consensus development conference.[6] This decision was based on the results of four liver transplant centers active at that time. One of these four pioneering centers was the Academic Hospital Groningen, nowadays known as University Medical Center of Groningen. In 1989, tacrolimus (TAC) was introduced.[7] TAC had a stronger immunosuppressive effect than CsA, a similar safety profile and fewer cosmetic side-effects.[8] Despite the development of new immunosuppressive drugs since then, TAC has remained the cornerstone of immunosuppressive therapy after pediatric liver transplantation in most transplantation centers.

From the beginning of transplantation medicine, however, it had been realized that immunosuppression comes with a price. Long-term immunosuppression is associated with an increased risk of infections and neoplastic diseases. Side effects of calcineurin blockers (TAC and CsA) include nephrotoxicity, neurotoxicity and hypertension. CsA is additionally associated with cosmetic side effect as hirsutism and gingival hyperplasia. Side effects of steroids are hypertension, stunting of linear growth and osteoporosis.

Apart from development in immunosuppression, advances in organ preservation, surgical techniques and peri-operative care have dramatically improved long-term patient and graft survival following liver transplantation. A patient survival above 80% at 10 years after pediatric liver transplantation has been reported.[9] Long term survival and quality of life is mainly determined by proper functioning of the liver graft and no or only minor side effects of immunosuppressive medication. As children have a longer life span following liver transplantation than patients who are transplanted at adult age, an even greater emphasis should be placed in the former on long-term prevention of end organ damage. Pediatric liver transplant recipients face the challenge of maintaining long-term graft function, while long-term immune and non-immune complications due to immunosuppressive medication should be minimized.

Aim and outline of the thesis

Pediatric medicine should evaluate its benefits and costs both in short and long term time frames. The same holds for pediatric liver transplantation, which is a rather new treatment modality. The aim of this thesis is to evaluate the consequences of various immunosuppressive regimens on (long-term) side effects and on graft histology after pediatric liver transplantation. The particular side effects which were studied were kidney function, growth retardation and infections with Epstein Barr Virus.

Immunosuppressive medication has been associated with a higher risk on post transplant malignancies. In children the most frequent malignancy is a post transplant lymphoproliferative disease (PTLD). PTLD is associated with Epstein Barr virus infection, which can develop into an uncontrolled lymphocyte proliferation. It has remained difficult to screen for PTLD. One possible screening tool involves the determination of the high EBV viral load in blood. We evaluated the prospective value of EBV viral load determinations in the first 6 months after pediatric liver transplantation, with respect to the development of a primary, symptomatic EBV infection or a PTLD (**Chapter 2 The value of prospective monitoring Epstein-Barr virus DNA in blood samples of pediatric liver transplantation recipients.)**

The transplantation program in Groningen was started in 1979, and the first child was transplanted in 1982. In 1986 Cyclosporine A was introduced in the standard immunosuppressive protocol. In 1999 CsA was substituted in the standard protocol by TAC. Patients transplanted before 1986 had done reasonably well with an immunosuppressive protocol consisting of cyclophosphamide, azathioprine and prednisolone. The 1986 protocol with CsA included controlled withdrawal of CsA at two years after transplantation to prevent long-term side effects, mainly renal damage. Withdrawal of CsA was only attempted when the patient and graft function were doing well and when liver biopsy at 2 years after transplantation did not show histological rejection. We evaluated the success rate of this protocol, with respect to occurrence of rejection, long term kidney function and plasma lipid concentrations in **chapter 3: Cyclosporin withdrawal after pediatric liver transplantation.**

One of the side effects of immunosuppression, especially steroids is linear growth retardation. This is of particular relevance since children with end stage liver disease frequently have already growth retardation (i.e. before liver transplantation). We evaluated growth and final height in children who underwent a liver transplantation between 1982 and 2000 (**chapter 4. Growth and final height after liver transplantation in childhood.)**

As stated above, pediatric liver transplantation is still a relatively new treatment. There is still a lack of long-term clinical and histological data. It still has remained unclear to what extent a pediatric liver transplantation is a permanent or a temporary solution. Peeters et al [10] described that 31% of the patients had mild portal fibrosis in their liver grafts in protocol biopsies at 1 year after pediatric liver transplantation. We evaluated the histological and clinical follow up of grafts and patients, respectively, up to 10 years after transplantation (**chapter 5: Graft fibrosis after pediatric liver transplantation, ten years of follow-up.**) For this study we used a cohort of patients who all were treated with a CsA based immunosuppressive regimen (1986-1996).

In 1999, the standard immunosuppressive protocol was adapted by replacing CsA by TAC. Since CsA was associated with a high frequency of graft fibrosis (Chapter 5), we questioned whether a similar phenomenon was observed in transplanted children on a TAC based immunosuppressive regimen (**chapter 6: High prevalence of histological hepatitis and portal fibrosis at 1 year after pediatric liver transplantation on a tacrolimus-based immunosuppressive regimen.**)
Chapter 7 concludes this thesis with a summary, a general discussion of the results of the studies, recommendations and future prospects.

References

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